REMARKS

This filing includes the submission herewith of a certified copy of priority document EPO 00201433.0, and a Request for Continued Examination (RCE) with fee.

Priority data has been added as new text at the beginning of the written description. This added text is not a new assertion of a priority claim, but merely an insertion of text consistent with this same, and previously, asserted priority claim that is already of record. *See, e.g.*, Transmittal Letter, p. 1, and Declaration and Power of Attorney, filed on august 18, 2000; US PTO Filing Receipt, mailed 09/29/2000 (asserting for the record and acknowledging priority claim).

A typographic correction has been introduced in claim 9, and this claim has been further amended to clarify its language and make it similar to the language used in other pending claims that recite a plurality of sequencing primers.

Amendments to claim 1 have been introduced to clarify its language, and to remove language redundancies.

Claims that were not elected in the response dated January 12, 2002, are withdrawn without prejudice of their reintroduction as deemed appropriate.

References to the Application given hereinbelow are provided by way of illustration, but not as an interpretive limitations.

1. Claim rejections under 35 U.S.C. § 112 ¶ 1

Applicants respectfully traverse the rejections of claims 1-9 under 35 U.S.C. § 112 ¶ 1. *See* Office Action, p. 7. As reasoned below, the recitation of outer primers in claim 1, and by incorporation in its dependent claims 2-9, satisfies the description requirements under 35 U.S.C. § 112 ¶ 1.

The Office Action asserts that the outer primer recited in claim 1 requires both SEQ ID No: 1 and SEQ ID No: 2. The Office Action asserts that the choice, as recited in claim 1 and by incorporation in its dependent claims, of either SEQ ID No:1 or SEQ ID No: 2 is "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Office Action, p. 7.

The application as filed, in contrast, describes amplification by using outer primers as represented in SEQ ID No: 1 and SEQ ID No: 2. *See, e.g.*, Application, p. 3. The application as filed describes "primers" –in plural– and then indicates SEQ ID No: 1 and SEQ ID No: 2 as such primers. Whereas SEQ ID No: 1 and SEQ ID No: 2 are encompassed within such group of primers as indicated in the Office Action, nothing in the application indicates that such possibility and only such possibility is to be considered in the context of this invention. In fact, such narrow interpretation would be inconsistent with the use of the term "primers" in plural, which refers to more than one possible primer. In addition, Table 1 lists individual primers, and SEQ ID No: 1 and SEQ ID No:2 are listed therein as individual primers. *See, e.g.*, Application, p. 11. Furthermore, the Application provides definitions and descriptive information on matters such as primers and amplification. *See, e.g.*, Application, p. 9, *et seq.*

As reasoned hereinabove, an interpretation of the written description concerning amplification by using outer primers as represented in SEQ ID No: 1 and SEQ ID No: 2 in light of the plain language in the application itself indicates that the possibility of using SEQ ID No: 1 or SEQ ID No: 2 was included in the description at the time of filing. Support in the specification as filed is therefore established.

It has not been established that one of ordinary skill in the art would not understand that this possibility is encompassed by the invention as described. Furthermore, "[e]ach claim must

be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." M.P.E.P. § 2163.II.A.1, p. 2100-159, 8th ed. (Aug. 2001).

Applicants have pointed out where and/or how the originally filed disclosure supports the amendments by referring to illustrative portions of the Application. In this context, it is established that if " 'the examiner finds that the disclosure does not reasonably convey that the inventor had possession of the subject matter of the amendment at the time of the filing of the application, the examiner has the initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.' " M.P.E.P. § 2163.II.A, p. 2100-159, 8th ed. (Aug. 2001) (quoting M.P.E.P. . § 2163.04).

Applicants respectfully submit that the claims comply with 35 U.S.C. § 112 ¶ 1, and request that the claim rejection pursuant to this authority be withdrawn.

2. Claim rejections under 35 U.S.C. § 112 ¶ 2

Applicants reassert the traverse of the rejection under 35 U.S.C. § 112 ¶ 2 of claim 4. Furthermore, it is respectfully pointed out that the Office Action does not properly characterize parts of the written description concerning subject matter that is claimed in claim 4. Claim 4 has been amended to further clarify the replacement recitation provided therein.

The Office Action asserts that the replacement primers are to be used when the original sequencing primers fail, and seems to attribute this requirement to the written description itself. In contrast, the written description refers to failure in the context of an example. See, *e.g.*, Application, p. 4, *ll.* 25-26.

The Office Action does not set forth why, in light of the examples provided in the written description and in light of the knowledge in the art about sequencing, a person of ordinary skill in the art would not understand the term "failure" as applied in this context. The

Office Action furthermore does not explain why a person of ordinary skill in the art in the same context would be incapable of ascertaining the metes and bounds of what is claimed in claim 4 when the written description provides, *inter alia*, that a "described primer that obtains sequence from the region that ... SEQ ID No: 8 ... was expected to cover can be used [with illustrative examples following in the original]". See, *e.g.*, Application, p. 4, *ll.* 26-28.

Applicants note that the "essential inquiry pertaining to ... [the] requirement [set forth in 35 U.S.C. § 112 ¶ 2] is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity", and that definiteness "must be analyzed, not in the vacuum, but in light of: (A) The content of the particular application disclosure; (B) The teachings of the prior art; and (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the art at the time the invention was made." M.P.E.P. § 2173.02, p. 2100-194, 8th ed. (Aug. 2001). It has not been established that the teachings provided in the Application, quoted in part hereinabove for illustrative purposes, do not satisfy the reasonableness standard set forth in the M.P.E.P., in light of the teachings in the Application, the ordinary skill in the art and the interpretation that would be given in such context by one of ordinary skill in the art.

Accordingly, Applicants respectfully submit that the claims comply with 35 U.S.C. § 112 ¶ 2, and request that the claim rejection pursuant to this authority be withdrawn.

3. Claim rejections under 35 U.S.C. § 103

Applicants reassert the grounds for traversal of this rejection as asserted in prior responses. In addition, Applicants respectfully submit that a *prima facie* case of obviousness has not been established for at least the following reasons.

The Office Action asserts that "the primers [are] obvious in view of the cited references" (Office Action, p. 4, 6). Even if, *arguendo*, the reasoning set forth in the Office Action that

precedes each one of these statements could show obviousness of these primers, it is noted that the pending claims are method claims that recite primers and operations performed with certain primers. A *prima facie* case of obviousness must therefore include a showing under 35 U.S.C. §103 of obviousness of the claimed subject matter where all the claim features are taken into consideration and each claim is viewed as a whole. *See, e.g.*, M.P.E.P. §§ 2141-43, . Arguments concerning the obviousness of composition of matter claims that are not part of the pending claims are merely not relevant.

An analysis of the references reveals, as also made of record in the Office Action and in the Office Action dated 02/27/2002, that the recited elements are not disclosed in their entirety by the cited references. Regarding subject matter in the pending claims, Hertogs[1] only discloses primers with SEQ ID No: 1 and SEQ ID No: 2, and the rest of the references do not even disclose these primers. Furthermore, it is not shown that the references that are cited in addition to Hertogs overcome the lack of disclosure found in Hertogs.

It is not established that the art of record teaches the claimed methods that comprise the use of replacement primers and their selection as presently claimed.

Therefore, the art of record, even if it were combinable, does not teach or suggest for at least the foregoing reasons all the claim limitations.

The Office Action seems to change the characterization of the disclosure in Hertogs from the statement that it "does not teach the sequences disclosed in SEQ ID No: 3-12" (Office Action dated 02/27/2002, p. 5) to the statement that the "amplification product [in Hertogs] comprises the sequences disclosed in SEQ ID 3-12". Office Action, p. 4. As of record in the Office Action dated 02/27/2002, Hertogs does not disclose or suggest SEQ ID 3-12. If disagreement with this statement is found, Applicants respectfully request that a cite to Hertogs

[1] Because the cited art has already been referred to in the form of full citations in the Office Actions, responses, and IDS material, only the first author's last name will hereinafter be used.

pointing out with specificity to such disclosure be provided. Furthermore, Hertogs does not disclose or suggest the use of the primers as recited in the pending claims.

Even if the statement that the amplification product in Hertogs comprises the sequences disclosed in SEQ ID 3-12 were correct, it would fail to establish a *prima facie* case of obviousness. It does not follow how one would perform the primary PCR product amplification as claimed on the basis of this statement. Applicants note that the primary PCR product contains anywhere between thousands to tens of thousands of possible primer sequences. The art of record fails to provide any disclosure or suggestion on how to recognize those to be used with an expectation of success.

In addition to the lack of disclosure in the art of record, the cited references disclose methodologies that rely on a variety of entirely different primers for the various PCR amplification steps. These disclosures, with their variety of primers that do not include the ones that are part of the presently claimed methodology, seem to be teaching away from the claimed subject matter because they provide a great variety of primers with no direction on how one could arrive at the claimed methods and with no direction on how to modify the reference teachings to arrive to such methods.

Applicants respectfully submit that the equivalence argument set forth in the Office action does not apply to the presently claimed methodologies. The "determination of mutations in the *pol* gene" that the Office Action relies on to characterize equivalence (Office Action, p. 5), is a statement of a complex problem as set forth in the present Application and also in the introductory sections of the cited references. *See, e.g.*, Application, p. 1, *ll.* 9-20; Hertogs, p. 269; Demeter, p. 94; Boden, headnote; Cabana, p. 480; Birk, p. 2370; Zazzi, p. 1; Kozal, cols. 1-2. This statement, however, is not a proof of equivalence and it is not a proof of prior-art-recognized equivalence.

The high mutagenicity of HIV makes the primer identification and use difficult. This is in part because if a given primer anneals a particular sequence in a region of the virus' genome that is mutagenic, the primer designed against the HIV wild type sequence will hardly anneal or not anneal at all when a mutation is present in the region to which the primer would otherwise normally anneal. This annealing failure will lead to an insignificant amount of PCR product or to no PCR product at all, which in turn leads to the failure of the assay methodologies that rely on such PCR amplification steps. The art fails to disclose or suggest how this problem can be addressed with any expectation of success as in the claimed methodologies. Absent the teachings provided in the present Application, the art fails to disclose or suggest that the selection of the method steps as presently claimed can lead to an assay methodology that encompasses the wide protease and RT region that is covered by the claimed methodologies.

As to the citation of *In re Ruff,* 256 F.2d 590, 118 U.S.P.Q. 340 (C.C.P.A. 1958), provided in the Office Action, it is respectfully submitted that this authority places a consideration of equivalence under the general guidelines for an analysis under 35 U.S.C. § 103. It is an analysis under 35 U.S.C. § 103 what must be followed for establishing a *prima facie* case of obviousness. *In re Ruff* establishes that "[a] safer guide ... to the issue of patentability ... is the patent statutes. This question of equivalence ... is a special aspect of what amounts to patentable 'invention', assuming novelty to exist. The statutory provision on this subject is 35 U.S.C. [§] 103 and the test there laid down is simply whether the difference between what is claimed *and the prior art* would have been obvious to one of ordinary skill in the art at the time the invention was made." 118 U.S.P.Q. 340, 347.[2] As established herein and in the previous responses and also as made of record in the Office Action and in the Office Action dated

[2] The M.P.E.P. itself supports the position established in *In re Ruff*, by providing that "[I]n order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents." M.P.E.P. § 2144.06.

 the prior art fails to disclose and suggest the claimed methodologies. The differences between what is claimed and the prior art teachings here are such that the prior art does not support a *prima facie* case of obviousness.

If the position in the Office Action is that the complexity of the high mutagenicity of HIV has been recognized by a plurality of research groups, then this recognition seems to support the nonobviousness of the claimed methodology, This is in part because no other research of record, other than the work in the present Application, has disclosed the claimed methodologies or suggested their adoption with any indication of success.

The Office Action uses generic expressions such as "sequencing the *pol* region", "determination of mutations in the *pol* gene" and "determining the sequence phenotype". Applicants respectfully note that the claimed subject matter has to be considered as recited in the claims, with the recited features and viewing each claim as a whole. Therefore, arguments that focus on characterizations such as those quoted above from the Office Action instead of on the actually claimed subject matter may not establish a *prima facie* case of obviousness. Furthermore, the analysis of teachings in the art about generic characterizations such as "sequencing the *pol* region", "determination of mutations in the *pol* gene" and "determining the sequence phenotype" might at best be helpful to ascertain capabilities of one of ordinary skill in the art, but even if, *arguendo*, such capabilities were properly ascertained, it is well established that the fact that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish *prima facie* obviousness. See, *e.g.*, M.P.E.P. § 2143.01.

Applicants respectfully note that the citation in the Office Action of *In re Baird*, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994) (Reversing holding of unpatentability under 35 U.S.C. § 103 by the US PTO Board of Patent Appeals and Interferences) does not support a *prima* facie case

of obviousness. On the contrary, and as reasoned below, this authority actually supports the rationale for nonobviousness of the pending claims.

In *In re Baird,* the claim at issue was directed to a flash fusible toner comprising a bisphenol A polyester binder resin. The reference that was cited as purportedly supporting the rejection of the claim as obvious disclosed a class of diphenols that comprised bisphenol A. *See In re Baird,* at 1551. The Board upheld the examiner's rejection that was based on the rationale that "bisphenol A 'may be easily derived from the generic formula of the diphenol in [the reference] and all the motivation the worker of ordinary skill in the art needs to arrive at the particular polyester of the instant claim [] is to follow [that formula].' " (Changes in the original). *In re Baird,* at 1551. The Board further added, " 'the fact that [the claimed] binder resin is clearly encompassed by the generic disclosure of Knapp ... provides ample motivation for the selection of [the claimed composition].' " (Changes in the original). *In re Baird,* at 1551. The Federal Circuit reversed the holding by the Board in light of the patentee's arguments that there was "no suggestion in ... [the reference] to select bisphenol A from the vast number of diphenols covered by the generic formula and that the Board thus erred in concluding that the claimed compounds would have been obvious." *In re Baird,* at 1551-52. The Federal Circuit reasoned that the reference did not render the claimed compounds obvious because, although the claimed compounds were encompassed in the reference disclosure, nothing in such reference disclosure suggested that one should select such compounds. *See In re Baird,* at 1552.

The Federal Circuit further reasoned that the reference actually appeared to teach away from the selection of the claimed compound by focusing on other diphenols. *See id.*

As part of the support for its argument, the Federal Circuit cites in *In re Belle,* 991 F.2d 781, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993), where the Federal Circuit again held that a DNA sequence would not have been obvious in view of reference prior art that suggested a large

number of possibilities and that failed to suggest why among all such possibilities one would seek the claimed sequence. *See In re Baird*, at 1552.

The pending claims recite subject matter that is not disclosed by the reference art. Because of this lack of disclosure, the present method claims are even farther from being *prima facie* obvious in light of the reference disclosures than the compounds claimed in *In re Baird* were in light of the reference teachings cited therein. As in *In re Baird*, the reference art does not provide any suggestion on selection of the claimed methodology and its features. Furthermore, as reasoned in *In re Belle*, the pending method claims may not be obvious when the claimed subject matter has not been disclosed or suggested in the prior art, and when the claimed subject matter includes features for which the prior art does not provide any teaching or suggestion on how one could seek such features out of a wide array of possibilities.

Applicants respectfully submit that a *prima facie* case of obviousness for the pending claims has not been established and respectfully request the withdrawal of this rejection.

4. New Claims

New claims 21 (independent) and 22-34 (dependent directly or indirectly form claim 21) have been added. These new claims recite, *inter alia*, either directly or by incorporation from independent claim 21, "a primer chosen from an outer primer with SEQ ID No:1 and SEQ ID No: 2". Therefore, these claims recite subject matter according to one of the teachings in the Application as filed, as referred to in the Office Action, and are therefore supported by the specification.

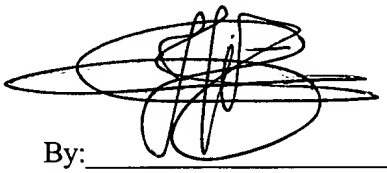
New claim 24 furthermore recites "wherein at least one of said replacement primers is at least one of from the group SEQ ID No: 13 and SEQ ID No: 14 for sequencing primer SEQ ID No: 7, SEQ ID No: 15 and SEQ ID No: 16 for sequencing primer SEQ ID No: 8, SEQ ID No: 16 and SEQ ID No: 17 for sequencing primer SEQ ID NO: 9, SEQ ID No: 4 and

SEQ ID No: 18 for sequencing primer SEQ ID NO: 10, SEQ ID No: 18 and SEQ ID No: 19 for sequencing primer SEQ ID NO: 11, and SEQ ID No: 20 and SEQ ID No: 21 for sequencing primer SEQ ID NO: 12". Therefore, this claim recites subject matter according to one of the teachings in the Application as filed, as referred to in the Office Action regarding claim 4, and is therefore supported by the specification.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page(s) is/are captioned "Version with markings to show changes made".

Applicants respectfully request early favorable action in this case.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Twice Amended) A method for detection of mutations in the *pol* gene of HIV-1 isolates comprising the steps of:

e) isolation of a sample comprising HIV-1 RNA,

f) PCR amplifying RNA from said sample using at least a primer chosen from [an] the outer primer [chosen from] group SEQ ID No: 1 [or] and SEQ ID No: 2, to obtain a primary PCR product,

g) PCR amplifying said primary PCR products using at least a 5' and 3' primer chosen from [an] the inner primer [chosen from] group SEQ ID No: 3, SEQ ID No: 4, SEQ ID NO: 5, [or] and SEQ ID No: 6, to obtain a secondary PCR product, and

h) sequencing said secondary PCR product.

2. (Twice Amended) A method according to Claim 1, wherein said secondary PCR product is sequenced using at least one sequencing primer chosen from the group SEQ ID No: 7, SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, [or] and SEQ ID No: 12.

3. (Unchanged) A method according to Claim 1, wherein said RNA is viron RNA extracted from said sample.

4. (Twice Amended) A method according to Claim 1, wherein said secondary PCR product is sequenced using at least one sequencing primer chosen from the group SEQ ID NO: 7, SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, [or] and SEQ ID No: 12; and

wherein at least one of said sequencing primer is replaced by one or a pair of replacement primers, wherein said one or a pair of replacement primers obtain sequence from the region that said at least one sequencing primer is expected to cover.

5. (Twice Amended) A method according to Claim 1, wherein said secondary PCR product is sequenced using at least one sequencing primer chosen from primers up to 1, 2, 3, or 4 nucleotides upstream or downstream primer regions chosen from the group SEQ ID No: 7, SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, [or] and SEQ ID No: 12.

6. (Twice Amended) A method according to Claim 1, wherein the outer primer is chosen from primers up to 1, 2, 3, or 4 nucleotides upstream or downstream primer regions chosen from the group SEQ ID No: 1 [or] and SEQ ID No: 2.

7. (Twice Amended) A method according to Claim 1, wherein the inner primer is chosen from primers up to 1, 2, 3, or 4 nucleotides upstream or downstream primers regions chosen from the group SEQ ID No: 3, SEQ ID No: 4, SEQ ID No: 5, [or] and SEQ ID No: 6.

9. (Twice Amended) A method according to Claim[s] 1, wherein said primary PCR product is sequenced using at least one sequencing primer chosen from [any] the group SEQ ID No: 7, [to 12] SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, and SEQ ID No: 12.